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Request for grant of a patent

The Patent Office
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South Wales NP10 8QQ

1. Your reference
1908601/AM

2. Patent Application Number
0402323.0

0 3 FEB 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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8606295001

Patents ADP number *(if known)*

If the applicant is a corporate body, give the country/state of its incorporation

Country: **England**
State:

4. Title of the invention

Measurement of Analytes in Gas and/or breath

5. Name of agent
"Address for Service" in the United Kingdom to which all correspondence should be sent

Beresford & Co
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London WC1V 6BX

Patents ADP number

1826001

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Description	4
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents form 7/77)*	**1 + 3 copies**
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Signature Beresford & Co — Date 3 February 2004

BERESFORD & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

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Patent Disclosure

Measurement of Analytes in Gas and/or Breath

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Introduction

When seeking to measure the concentration of various analytes in the mammalian body a number of different physiological fluids are typically sampled. For the vast majority of routine clinical measurements, for example for glucose, blood is the preferred fluid, as in the majority of cases this provides the most clinically relevant measure. However, analytical regimes that require blood (or plasma) samples, whether they are capillary, arterial, or venous require by definition that the skin is punctured to gain access to the sample. This introduces a number of issues, pain associated with sampling, risk of infection both to the patient and potentially to the caregiver, cost, etc.

Hence, sampling of a vast number of different fluids has been used to avoid the need to puncture the skin. These can be divided into two principal categories, non-invasive and minimally invasive. Most of the non-invasive methods involve irradiation (using various wavelengths) of the skin or body and inferring the concentration of the analyte of interest from the resultant modulated signal. With the possible exception of pulse oximetry for the measurement of oxygen saturation, these systems generally have insufficient performance for clinical or practical use. Minimally invasive techniques for sampling abound and include the use of such fluids as urine, saliva, sweat and tears. Such samples have the general characteristics of exhibiting attenuation in concentration and delay in changes in concentration in respect to the blood and often represent an integration of the blood concentration over some period. Whilst such samples are wholly adequate for some purposes, many applications require a more accurate and more current estimate of the prevailing blood concentration of the analyte of interest.

One fluid that has not been used greatly on a routine basis for estimation of blood concentration of analytes is the exhaled breath. A few notable exceptions do exist such as the "breathalyser" for estimation of the alcohol concentration in blood and the estimation of arterial carbon dioxide concentration by measuring the absorption of infra red irradiation using a technique called "end-tidal CO2 measurement".

Measurement of breath borne analytes has the advantages of the breath concentration being closely related to the blood concentration at the alveoli and has the potential to measure rapid changes in real time. The limitations are fairly significant such as the

concentration of most analytes of interest in the breath are extremely low, certain metabolites such as glucose are effectively absent, as they cannot pass across the alveoli.

Measurement of certain drugs and analytes of clinical interest that are currently either not measured or the sampling system utilises an invasive methodology could, potentially, be measured in the exhaled breath by an appropriate sensing system.

Concept

It is proposed that the concentration of an analyte of interest, one example being the intravenous anaesthetic propofol, can be measured directly in exhaled breath using a chemical sensor placed in or near the airway.

For clinical use the sensor would ideally be a microsensor placed into the endotrachael tube, anaesthetic circuit or ventilator circuit. The microsensor could operate in a number of physicochemical principles, including, but not limited to, amperometric, potentiometric, gravimetric, thermal or conductimetric. Additionally, as propofol is known to fluoresce an optical sensor such as a fibre optic device, a suitable detector, an optically coupled chip or by measurement non-invasively by transmitted or reflected light could also be employed.

Further purification and concentration of the drug can be achieved *in situ* by encapsulating or covering the sensing elements in a material, solid or liquid, into which propofol preferentially partitions over the medium it is in.

Specific recognition molecules may be found or more likely designed and fabricated such as molecularly imprinted polymers, other synthetic or artificially created receptors that have a high binding affinity for the analyte of interest, i.e., preferentially bind the molecule of interest such as propofol.

The binding of the analyte molecule can be a direct concentration step allowing detection by a number of means, optical, electrochemical, conductimetric, gravimetric or spectroscopic, to name but a few. It is also possible that the specific binding event causes a physico-chemical change detectable by a standard sensor transduction technique such as, but not limited to, potentiometry, amperometry, conductimetry, and spectroscopy, chromatography, capacitance and micro-balances, resonant sensors, thermal methods and calorimetry.

By simultaneously measuring concentrations of the analyte of interest in other tissues, fluids or body compartments it is possible to determine the kinetic profile of analytes within the body. Potentially, an extremely useful approach would be to measure either separately or simultaneously related metabolites of the analyte of interest to give information on the physiological passage/pharmacokinetics of the analyte.

Information derived from such a sensing system could be used to provide the input for closed-loop drug administration when coupled with the appropriate administration device and control algorithm.

Additionally, it may be advantageous to agitate and/or oscillate the exhaled air in the artificial airway to aid diffusion of the analytes of interest from the alveolus and facilitate greater concentration of the analyte at the sensor.

One potential embodiment of the invention.

Using these general ideas a sensor for the specific measurement of the intravenous anaesthetic propofol and/or its metabolites in exhaled breath is envisaged, see Figure 1.

A microsensor, substantially fabricated from silicon, uses a synthetic receptor i.e., a material designed and fabricated to bind the propofol and/or its derivatives, a non-aqueous fluid over the sensor to concentrate the propofol and/or its derivatives in the exhaled breath. The propofol and its derivatives in the breath preferentially partition into the fluid covering the microsensor and diffuse towards the MIP. The molecularly imprinted polymer binds the analyte causing a physiochemical change that is detected by the transducer which in turn creates an electronic signal proportional to the concentration of the analyte present.

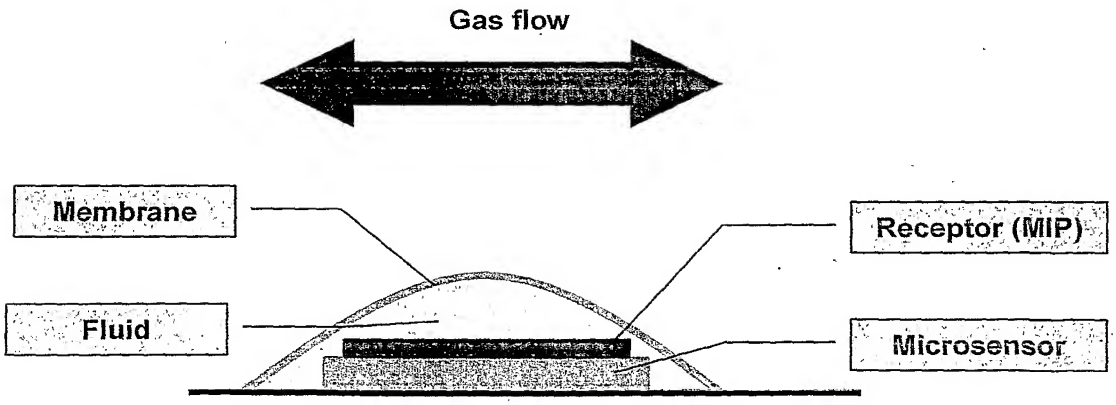

Figure 1. Concept sensor

In addition to single parameter measurements multi-parametric analysis of breath borne analytes could prove useful, for example to facilitate concurrent analysis of:

- The analyte of interest and its metabolic derivatives
- Analyte of interest and interfering substances
- Analyte and background signal
- Any combination of the above

Thus, it would be possible to compensate for various potential causes of potential sensor inaccuracy, drift, specificity, etc as well as gaining a more complete view of the status of the patient.

One particular example of a silicon-based microsensor chip with multiple chemical sensor elements is shown in Figure 2. However, the invention is not limited to multi-parametric micromachined chemical sensors and can employ a wide range of other microscopic and macroscopic sensors.

The sensor elements may for example employ electrochemical (e.g. potentiometric, in particular ISFETs (ion-sensitive field effect transistors) or amperometric), conductimetric, optical, gravimetric, surface-acoustic waves, resonant or thermal principles.

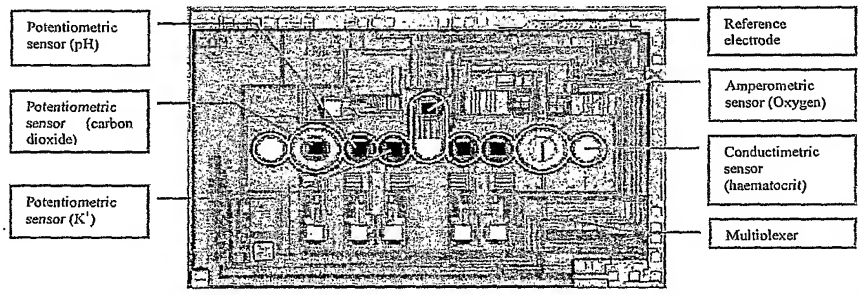

Figure 2: Example of a multi-parameter chemical sensor chip developed by Sphere Medical Ltd.

One method by which to functionalise the different transducers on the multi-parametric chip is by the use of pool-like structures on the device substrate around one or more of the transducers. The structures may be circular or of any general shape which will be suited to the application in hand. In general, the shape of the structures will be chosen to suit the size and shape of the transducers. These structures would act to contain the mixture of some or all of the reagents that will be used to create the synthetic receptor(s), and/or the partitioning material and/or membrane of the device or sensor.